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ORIGINAL ARTICLE

Preoperative assessment of language areas in epileptic patients using functional MR imaging

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KEYWORDS

Functional magnetic resonance imaging;
Medical intractable epilepsy

Abstract *Objective:* To determine the role of functional magnetic resonance imaging (fMRI) in assessing hemispheric language dominance in patients with epilepsy who are candidates for surgical treatment.
Patients and methods: This study was conducted on (14) consecutively enrolled epileptic patients (12 males, 2 females; mean age, 21 years; range 16–58 years) who were prospectively examined by the neurologist. Eleven (78.6%) patients were dominantly right handed, three (21.4%) were dominantly left handed. All of them underwent language assessment with fMRI and the results were compared with the intraoperative direct electrical stimulation mapping recordings.
Results: In all the 14 epilepsy cases, language mapping data was concordant between fMRI and intraoperative direct electrocortical stimulation recordings for language dominance. However, fMRI mapping allowed for discrete, focal localization of regions involved in language processes whereas electrical recordings only delineated hemispheric dominance.
Conclusion: fMRI is considered as a powerful pre-surgical planning tool that has the potential to replace invasive and costly conventional methods. FMRI maps can easily be uploaded and used intra-operatively during stereotactic neurosurgery for accurate localization of complex brain functions.

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1. Introduction

Before surgery is performed for epilepsy or for neoplasm resection, localization of eloquent areas in the brain is important (1–3). Preoperative functional MR imaging (fMRI) localization of language functions is a promising tool to improve the treatment of pre- and postsurgical epileptic patients (3). Although neuropsychological assessment can contribute to the determination of language lateralization, neuropsychological tests alone are not sufficient to determine functional brain organization. Therefore, neuropsychological assessment is often combined with other tests (4,5).

The procedures most often used to assess eloquent areas of the brain are the Wada test and direct electrical stimulation (3–6). The Wada test involves injection of amobarbital sodium into the carotid artery (2), conventional angiography performed with iodinated contrast material, and imaging with ionizing radiation—all of which incur risks to the patient. The Wada test also requires the participation of a large medical team with both an angiographic component and a neuroscientific component. The use of the Wada procedure has been debated recently (6,7), because it is an invasive procedure and several severe complications, such as carotid dissection or arterial spasm, have been reported. Furthermore, the validity of the test itself has been questioned (7–12).

Direct electrical stimulation involves surgical placement of electrodes, with risks of infection and bleeding to the patient. Direct electrical stimulation also requires the participation of a large medical team, including the neuroscientific component and neurosurgical component (2).

Functional magnetic resonance (MR) imaging, which does not require the use of exogenous contrast material or catheterization, is a noninvasive alternative method for evaluation of eloquent areas of the brain. Functional MR imaging is less time-consuming and requires no postprocedural recovery time (6).

The aim of our study is to determine the role of functional magnetic resonance imaging (fMRI) in assessing hemispheric language dominance in Arab speaking patients with epilepsy who are candidates for surgical treatment and to show if it can replace other invasive tests.

2. Patients and methods

2.1. Patients

The study was done on 14 Arab speaking patients (12 males and 2 females) in a private center between 2009 and 2010. The inclusion of patients in this study was based on the following criteria: history of medically intractable epilepsy (exclusion of the patients with other associated lesions as tumors), consideration for surgical treatment, and the need for defining eloquent brain areas.

The mean age of the included patients in this study was 21 years and the age range was 16–58 years. Twelve (85.7%) male and two (14.3%) female patients were included. Eleven patients (78.6%) had right-hand dominance and three (21.4%) had left-handed dominance.

All the patients had undergone both fMRI and intraoperative electrocortical stimulation mapping.

All patients were alert and able to follow instructions well. All patients were seizure free for more than 24 h, and functional MR imaging tests were performed without sedation. Informed consent was obtained from the patient or the parent or guardian in all the patients who were examined.

2.2. Functional MRI imaging (Figs. 1–4)

After the procedure was explained to the patient and parent or guardian, the audiovisual system was tested. The auditory stimulus was delivered from a personal computer that used prerecorded sound files. A transducer located inside the room provided the sound to be transmitted to the patient's ears via tubes and MR imaging-compatible earphones. The visual paradigm was delivered through MR imaging-compatible scene.

Imaging was performed on a 1.5T scanner (Intera Philips). An 8-channel head coil was used for reception of the signal intensity. For anatomic reference, a high-resolution T1-weighted 3D fast radio-frequency spoiled gradient-recalled acquisition in the steady state with an inversion-recovery prepulse sequence was used (TR/TE/TI, 9.7/4.6/400 ms; parallel imaging [array special sensitive encoding technique ASSET] acceleration factor = 2, matrix = 208×170, FOV = 23 cm, section thickness = 0.8 mm, 260 contiguous sections). Acquisition time was 5:25 min. For functional imaging, a $T2^*$-weighted gradient-echo echo-planar imaging (EPI) sequence was used (TR/TE = 2000/45 ms, matrix = 64×64, FOV = 22 cm, section thickness = 5 mm, 50 contiguous sections). Acquisition time was 5:6 min per functional run, including 5 dummy scans that were discarded from analysis.

Functional MR imaging language paradigms included: word generation, word antonym, sentence generation, object naming, text reading and story listening.

2.2.1. Word generation

In which special words acting as titles were presented to the patient on a screen on which patients could see while lying in the MR scanner via a mirror and the patient was asked to think about different items under these titles with each title presented to the patient for 4 s with 36 s for activation and 18 s for rest, during rest patients were asked to concentrate on a small cross and try to relax.

2.2.2. Word antonym

In which words were presented to the patient in the same way and patients were asked to think about their antonyms, each word was presented to the patient for 2 s with 20 s for activation and 20 s for rest, during rest patients were asked to concentrate on a small cross and try to relax.

2.2.3. Story telling

In which short stories were presented to the patients via a special audio-system connected to a computer with 20 s for activation and 20 s for rest, during rest no sounds were presented to the patient.

2.2.4. Text reading

In which short paragraphs in Arabic language were presented to the patients on the screen with 20 s for activation and 20 s for rest, during rest symbolic transformation of the text was presented to the patient.

2.2.5. Sentence generation

In which the patient is asked to make sentences talking about the images presented to the patient on a screen which patients could see while lying in the MR scanner via a mirror with each image presented to the patient for 4 s with 20 s for activation and 20 s for rest, during rest patients were asked to concentrate on a small cross and try to relax.

2.2.6. Object naming

In which the patient is asked to name the objects within the images presented to the patient on a screen which patients could see while lying in the MR scanner via a mirror with each image presented to the patient for 4 s with 20 s for activation

Table 1 The choice of functional MRI tasks to be performed by the patient based on the age of the patient and his medical condition.

Patient	Word generation	Word antonym	Story telling	Text reading	Sentence generation	Object naming
1	+	+		+		
2	+	+		+		
3	+	+		+		
4					+	+
5	+	+		+		
6			+			+
7	+	+		+		
8	+	+		+		
9	+	+		+		
10	+	+		+		
11					+	+
12	+	+		+		
13			+			+
14	+	+		+		

and 20 s for rest, during rest patients were asked to concentrate on a small cross and try to relax.

The choice of the paradigms used for each case depends on the age and educational level.

Each paradigm consists of three runs of activity (20 s for each) alternating with three runs of rest (20 s for each).

The choice of functional MRI tasks to be performed by the patient was based on the age of the patient and his medical condition that might limit his ability to perform motor tasks and also his degree of literacy that might affect performing some language paradigms was listed in Table 1 as follows:

- Word generation, word antonym and text reading are suitable for adult educated patients.
- Story telling, sentence generation and object naming are suitable for children and illiterate patients.

The patient was briefly trained and tested with similar exercises before the procedure to ensure comprehension and good performance of the tasks.

Processing and analysis of fMRI data were performed off-line. The $T2^*$-weighted functional images were realigned to correct for the subject's motion during data acquisition. Functional and anatomic images were coregistered. Individual statistical parametric maps were calculated by using the general linear model by modeling the ''active'' and ''rest'' conditions as a boxcar function convolved with the hemodynamic response function. A t-contrast was then calculated for the ''active'' minus the ''rest'' condition.

2.3. Intraoperative electrical stimulation

Direct electrical cortical stimulation was done intraoperatively for all patients for detection of the Brocas area in the inferior frontal region and Wernicks area in the posterior temporal region by using subdural electrodes for stimulation and the recordings were detected and then compared to the fMRI results.

3. Results

This study was done on 14 intractable temporal lobe epilepsy (TLE) patients (12 males, 2 females) who underwent both fMRI language mapping and intraoperative electrical stimulation for pre-surgical planning purposes.

Table 2 Demographic data of the examined patients in this study.

Data	Numbers
Number of the males	12
Number of the females	2
Age range	16–58 years
Mean age	21
Left handed	3
Right handed	11

The demographic criteria of the patients were listed in Table 2.

The choice of functional MRI tasks to be performed by the patient based on the age of the patient and his medical condition was listed in Table 1.

The anatomic localization or lateralization of both the receptive (Wernicks) area and the expressive (Broca) area were detected. The results of the fMRI examinations were given to the neurosurgeon and then we compare these fMRI data (language) obtained prior to surgical intervention that were used intraoperatively with the recordings of the intraoperative electrical stimulation.

In all 14 epilepsy cases, language mapping data were concordant between fMRI and intraoperative electrical stimulation recordings with a sensitivity of 100% for both techniques.

However, fMRI mapping allowed for discrete, focal localization of regions involved in the language processes (Figs. 1–4), whereas electrical stimulation mapping only delineated hemispheric dominance.

FMRI maps can easily be uploaded and used intra-operatively during stereotactic neurosurgery for accurate localization of complex brain functions.

4. Discussion

Brain surgery has proved to be an effective treatment for individuals with medically intractable epilepsy, particularly for those patients with a single seizure focus (2,8). It is important to map lesions that are located in close proximity to critical

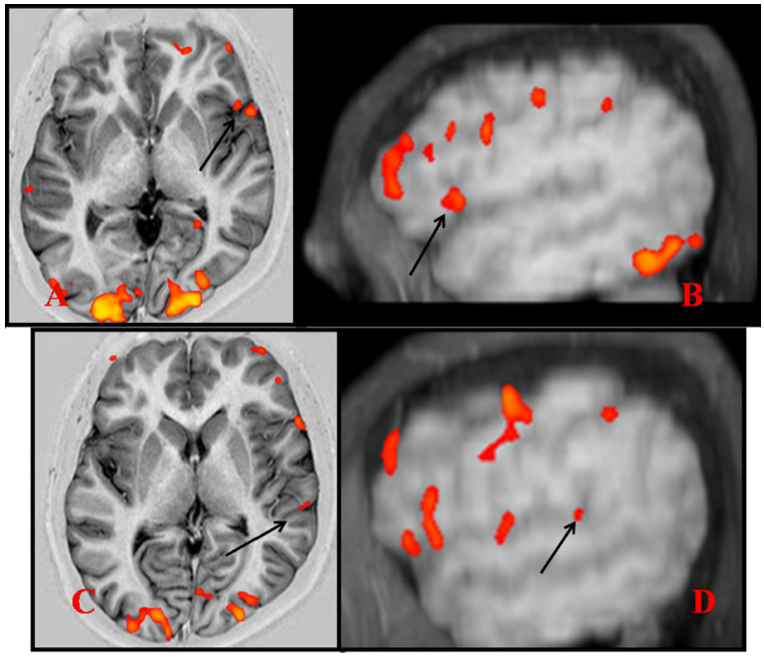

Figure 1 A 16 years old right handed male patient with convulsions started 2 years ago not responding to medical treatment, conventional MRI (not shown) showed no abnormality, EEG revealed left sided epileptic focus. Axial (A) and sagittal (B) views of fMRI paradigm for language revealed left sided representation of the Broca's area in its normal anatomic site (arrow). Axial (C) and sagittal (D) views of fMRI paradigm for language revealed left sided representation of the Wernick's area in its normal anatomic site (arrow).

areas of the brain because of the proximity of the pathologic condition to functional regions (1–3) and because reorganization of the brain functions may be transferred to other areas in the ipsilateral or contralateral hemispheres (13,14). Surgical resection of such epileptogenic lesions requires knowledge of the location of the brain functions of bordering areas to provide a better outcome, preferably without neurologic deficit (3).

Patients with lesions in or near the eloquent cortex typically undergo one of several invasive techniques to prevent loss of function following surgery. One of the most promising potential clinical applications of functional magnetic resonance imaging (fMRI) is to map these functions as part of the pre-surgical work-up to identify patients at-risk, guide the surgical entry, or tailor the surgical procedure to prevent deficits. While motor and sensory mapping are relatively straightforward, language mapping is far more complex. The language system is variable in location across individuals and in many cases may reorganize partially or completely to the contralateral hemisphere. In addition, multiple regions of the brain contribute to language functioning including essential regions that must not be removed in surgery, and contributory regions that may result in transient or insignificant impairments post-surgery. Despite these challenges, an increasing number of studies have supported the use of fMRI for pre-surgical language mapping in a variety of disorders (15).

Noninvasive functional MR imaging that relies on the blood oxygen level-dependent effect has been used to depict functional brain tissue (2,3,8–12). The blood oxygen level-dependent effect mechanism relies on the fact that an increase in regional cortical blood flow occurs in response to task performance from stimulation but this is not accompanied by a concomitant increase in local tissue oxygen extraction (2,11). The increased cerebral perfusion causes a paradoxical decrease in the concentration of deoxyhemoglobin (2). Oxyhemoglobin is diamagnetic, whereas deoxyhemoglobin is paramagnetic (2,11). The paramagnetic properties of deoxyhemoglobin create local field inhomogeneities, which decrease the signal intensity on T2- and T2*-weighted images (2,16). An increase in the level of venous blood oxygenation, therefore, is associated with a decrease in deoxyhemoglobin levels and an increase in MR imaging signal intensity (2,11). This change in signal intensity can be detected with magnetic susceptibility-sensitive imaging sequences, such as gradient-echo and echo-planar imaging (2).

Since its introduction, functional MR imaging has been investigated for presurgical mapping as an alternative for the invasive tests—Wada testing and direct electrical stimulation mapping. Investigators in several studies have compared mapping with functional MR imaging with Wada testing and direct electrical stimulation mapping (1–5). Functional MR imaging has been reported not only to be successful in mapping the main brain functions—including motor, sensory, and language functions—but also to correlate well with both Wada testing and electrocortical mapping (2,8–12).

In this study, all the included 14 epilepsy cases had undergone both preoperative fMRI and intraoperative direct electrical stimulation mapping, it was found that all language mapping data was concordant between fMRI and intraoperative electrical stimulation recordings with 100% sensitivity for both techniques.

However, fMRI mapping allowed for discrete, focal localization of regions involved in language processes (Figs. 1–4), whereas electrical stimulation mapping only delineated hemi-

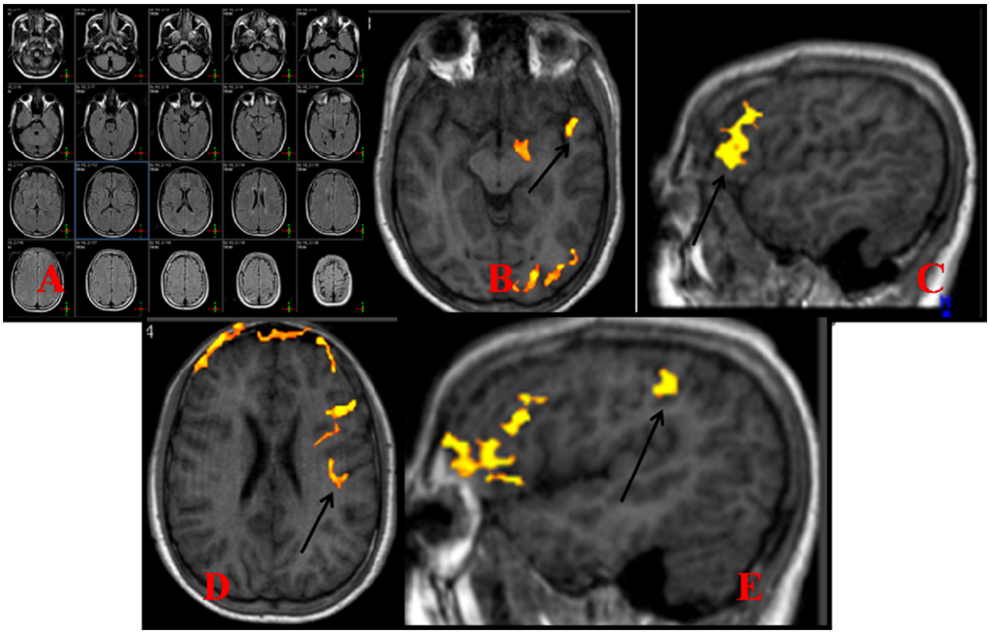

Figure 2 A 14 years old right handed female patient with convulsions started 6 years ago not responding to medical treatment, EEG revealed left sided epileptic focus. Axial FLAIR images (A) revealed no abnormality. Axial (B) and sagittal (C) views of fMRI paradigm for language revealed left sided representation of the Broca's area in its normal anatomic site (arrow). Axial (D) and sagittal (E) views of fMRI paradigm for language revealed left sided representation of the Wernick's area in its normal anatomical site (arrow).

spheric dominance. Finally, fMRI data can be used as the primary localization technique for the motor cortex, and was confirmed with electrophysiological recordings.

Researchers in prior studies focused on the evaluation of the diagnostic accuracy of functional MR imaging by comparing it with other techniques such as the Wada test and electro-

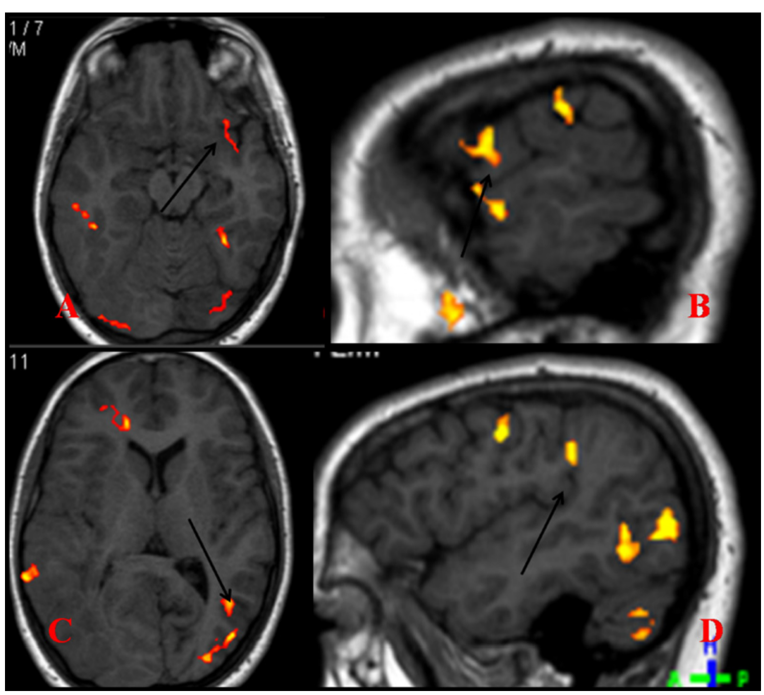

Figure 3 A 25 years old right handed male patient, drug abuser with convulsions started 3 years ago not responding to medical treatment, conventional MRI (not shown) showed mild generalized atrophic changes, EEG revealed left sided epileptic focus. Axial (A) and sagittal (B) views of fMRI paradigm for language revealed left sided representation of the Broca's area in its normal anatomic site (arrow). Axial (C) and sagittal (D) views of fMRI paradigm for language revealed left sided representation of the Wernick's area in its normal anatomic site (arrow).

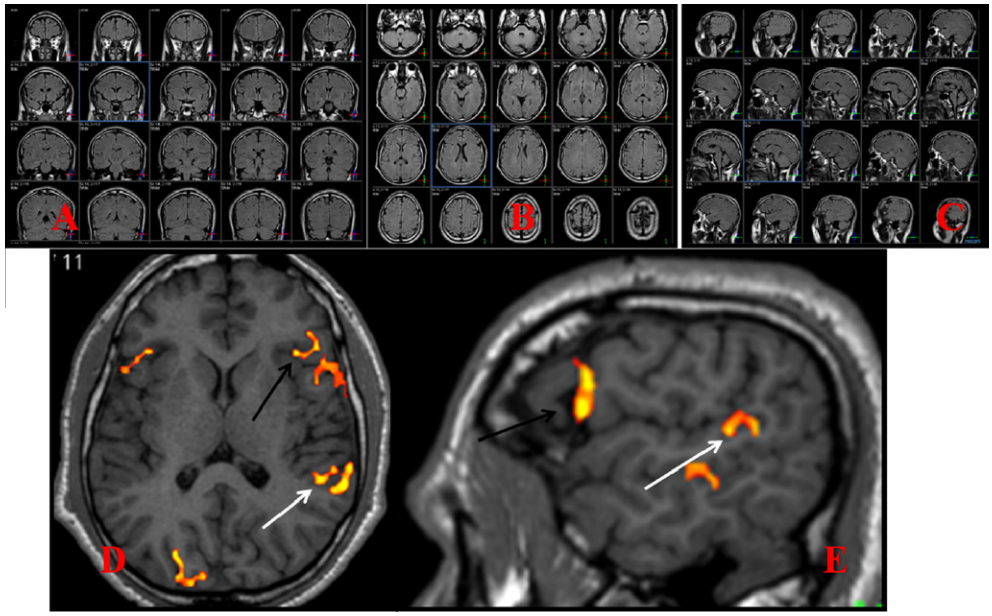

Figure 4 A 58 years old right handed male patient with convulsions started 1 year ago not responding to medical treatment, EEG revealed left sided epileptic focus. Coronal (A), axial (B) and sagittal (C) FLAIR images revealed no abnormality. Axial (D) and sagittal (E) views of fMRI paradigm for language revealed left sided representation of both Broca's (black arrow) and Wernick's (white arrows) areas in their normal anatomical site.

cortical stimulation, these estimated the clinical efficacy of functional MR imaging. There is limited information, however, about how the seizure team uses the information provided by functional MR imaging and, hence, how this information affects diagnostic thinking and decision making. The latter question is important in determining the value of the imaging study because the goal of any imaging study is to guide the seizure team in the treatment of the patient and ultimately to acquire better patient-based outcomes (1). We could not comment on this in our study as we did not follow the decision of the neurosurgeon before and after reading the MRI examination reports as our main aim was to detect the efficiency of fMRI in characterization of language areas.

Preoperative fMRI can predict naming outcome in patients undergoing epilepsy surgery. This finding has enormous potential clinical significance because it suggests that fMRI could be used to stratify patients in terms of risk, potentially allowing patients and physicians to more accurately weigh the risks and benefits of the surgery (17). Our study could not assess this point as there was no neuropsychological follow up for the patients naming outcome postoperatively because some of them follow up in other centers.

Several limitations, however, need to be considered. The first of them is the relatively small number of cases but we hope with growing awareness of the importance of the technique to have increased referral. The second one is that we spend a relatively long time in building up and optimizing our protocol especially the paradigms used to study language centers as—for our knowledge—this is one of the very first times to do these paradigms using Arabic language and to be used for Arab patients. Considerable efforts were also necessary in teaching and training the patient how to deal with the different paradigms especially as some of them had disturbed the conscious level. The third one is the lack of correlation with surgical outcome and with surgeon decision making, as our aim of this study is to establish our protocol so we are planning to continue our research and expand our team to include the referring physicians and epilepsy surgeons. Lastly, is the current lack of a robust way to convey our information to the neurosurgeon in his suit as an integrated part that could be superimposed on his surgical viewing, currently we provide images on films or CD as any other standard imaging procedure, the programs for better optimal use of our data are available but need financial support once our case load and referral increase.

In conclusion, we demonstrate the effectiveness of fMRI as a powerful pre-surgical planning tool that has the potential to replace invasive and costly conventional methods. FMRI maps can easily be uploaded and used intra-operatively during stereotactic neurosurgery for accurate localization of complex brain functions.

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